

**REMARKS/ARGUMENTS**

Status of Claims

Claims 1-20 are pending in the application. Claims 9 and 21-26 are subject to restriction and/or election requirement and have been withdrawn. Claims 1 and 10 have been amended. Claims, 2-8, and 15-20 have been canceled.

Status of Withdrawn Claims

Applicants' attorney respectfully submits that claims 15-20 were canceled in favor of rewritten claims 21-26. Consequently claims 21-26 are also subject to rejoinder, if the claims to the elected invention are found allowable.

Amendments to the Claims

Claims 1 and 10 have been amended to clarify the claimed invention. This amendment is submitted to clarify what applicant regards as his invention and does not introduce new matter into the claim. Applicant reserves the right to present the subject matter removed from these claims in a continuation application. Accordingly consideration and entry of this amendment is requested.

Objection to Claim

Claim 8 has been objected because of a typographic error. However, in view of the cancellation of claim 8 this objection is respectfully submitted to be moot.

Rejection of the Claims under 35 U.S.C. §112

Claims 1-8 and 11-14 were rejected under 35 U.S.C. §112, first paragraph, because the specification 1) while being enabling for making the claimed compounds does not reasonably provide enablement for making prodrugs of the claimed compounds; 2) enable one of skilled in the art of medicinal chemistry to use such prodrugs. Applicants' attorney notes this rejection is moot in view of the amendment of the claims. Accordingly, applicants' attorney respectfully requests reconsideration and withdrawal of this rejection.

Rejection under 35.U.S.C. §103

1. Claims 1-8 and 10-14 have been rejected under 35 U.S.C. §103 as being unpatentable over WO 97/25988 (Iyengar et al.) in view of US patent 6,197,772 B1 (Janssens et al.).

Iyengar et al. describes the combination of a specific tachykinin receptor antagonist with analgesics for the treatment of pain or prevention of pain or nociception. Janssens et al., which is a significant contribution to the art, describes substance P antagonist, including the claimed compound. However, neither of these documents suggest or teach that (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide can be used to reduce respiratory depression which is a common side effect of opioid therapy.

Respiratory depression appears to occur through opioids causing a  $\mu$ -opioid receptors-mediated blockade of specialized respiratory neurons receptors in the brainstem. Respiratory depression is significant issue in the management of pain with opioids because patients quickly become tolerant to the effects of opioids and require ever increasing doses of opioids to obtain pain relief. It is not uncommon for patients taking high doses of opioids to die of respiratory depression. Example C3 describes a test of the claimed compound in combination with an opioid in three different animal models gerbils, guinea pigs and rats. The data on gerbils indicated that the claimed compound reduced part of the respiratory depression induced by opioids. Opioid excitation is believed to be one of the mechanisms of respiratory depression. However, in two of the animals tested (guinea pigs and rats) opioids do not cause excitation. These two animals also showed reduced respiratory depression when treated with opioids (See ExampleC3).

Applicants' attorney respectfully submits that neither, Iyengar et al. or Janssens et al. suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids. Consequently, applicants' attorney respectfully submits that the presently claimed composition unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record. Accordingly, applicants' attorney respectfully submits that the present invention is patentable over the art of record.

2. Claims 1-8 and 10-13 have been rejected under 35 U.S.C. §103 as being unpatentable over US patent 5,880,132 (Hill) in view of US patent 6,197,772 B1 (Janssens et al.). However, applicants' attorney respectfully requests reconsideration of this rejection.

Hill describes tachykinin antagonist and opioid for treating pain or nociception. Janssens et al., which is a significant contribution to the art, describes substance P antagonists, including the claimed compound. Hill, however, does indicate in column 2, line 65 through column 3, line 3, that some of the side effects of opioid analgesic (such as respiratory depression, constipation, nausea and vomiting, etc.) can be reduced by using sub-maximal doses of the opioid analgesic. A similar point is made in column 28, lines 39-49 of Hill also discusses using reduced dosage levels of opioids. The additive effect of NK-1 receptor antagonist and opioid analgesics is further discussed in the examples in column 51 lines 51-60. However, neither of these documents suggest or teach that (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide can be used to reduce respiratory depression which is a common side effect of opioid therapy.

Respiratory depression appears to occur through opioids causing a  $\mu$ -opioid receptors-mediated blockade of specialized respiratory neurons receptors in the brainstem. Respiratory depression is significant issue in the management of pain with opioids because patients quickly become tolerant to the effects of opioids and require ever increasing doses of opioids to obtain pain relief. It is not uncommon for patients taking high doses of opioids to die of respiratory depression. Applicants' attorney respectfully submits that neither, Hill or Janssens et al. suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids. Consequently, applicants' attorney respectfully submits that the presently claimed composition unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record. Accordingly, applicants' attorney respectfully submits that the present invention is patentable over the art of record.

3. Claims 1-8, and 10-13 are rejected under 35 U.S.C. §103(a) as being unpatentable over US patent application publication 2002/0052504 (Elliott) in view of US 6,197,772 (Janssens et al.). However, applicants' attorney respectfully requests reconsideration of this rejection.

Elliott describes a tachykinin antagonist having a significantly different structure for the compound of the present invention. Elliott indicates on page 4, in paragraph 50 that substance P antagonists may be used in the treatment of respiratory diseases particularly those associated with excess mucus such as chronic obstructive airway disease, bronchopneumonia chronic bronchitis cystic fibrosis and asthma, adult respiratory distress syndrome, bronchospasm and cough. Elliott suggests that the compounds described therein can be combined with other

analgesics such as opioids. Janessens et al., which is a significant contribution to the art, describes substance P antagonist, including the claimed compound. However, neither of these documents suggest or teach that (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-dimethylphenyl)-1-piperazine acetamide can be used to reduce respiratory depression which is a common side effect of opioid therapy.

Respiratory depression appears to occur through opioids causing a  $\mu$ -opioid receptors-mediated blockade of specialized respiratory neurons receptors in the brainstem. Respiratory depression is significant issue in the management of pain with opioids because patients quickly become tolerant to the effects of opioids and require ever increasing doses of opioids to obtain pain relief. It is not uncommon for patients taking high doses of opioids to die of respiratory depression. Applicants' attorney respectfully submits that neither, Elliott or Janssens et al. suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids. Consequently, applicants' attorney respectfully submits that the presently claimed composition unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record. Accordingly, applicants' attorney respectfully submits that the present invention is patentable over the art of record.

4. Claims 1-8, and 10-13 are rejected under 35 U.S.C. §103(a) as being unpatentable over US patent 6,138,824 (MacLeod et al.) in view of US 6,197,772 (Janssens et al.).

MacLeod et al. describes 1-piperidinyl-propan-2-derivatives having a significantly different structure for the compound of the present invention. MacLeod et al. indicates in column 8, lines 5-10 that substance P antagonists may be used in the treatment of respiratory diseases particularly those associated with excess mucus such as chronic obstructive airway disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, bronchospasm and cough. MacLeod et al. suggests that the compounds described therein can be combined with other analgesics such as opioids. Janessens et al., which is a significant contribution to the art, describes substance P antagonist, including the claimed compound. However, neither of these documents suggest or teach that (+)-(B)-*trans*-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-*N*-(2,6-

dimethylphenyl)-1-piperazine acetamide can be used to reduce respiratory depression which is a common side effect of opioid therapy.

Respiratory depression appears to occur through opioids causing  $\mu$ -opioid receptors-mediated blockade of specialized respiratory neurons receptors in the brainstem. Respiratory depression is significant issue in the management of pain with opioids because patients quickly become tolerant to the effects of opioids and require ever increasing doses of opioids to obtain pain relief. It is not uncommon for patients taking high doses of opioids to die of respiratory depression. Applicants' attorney respectfully submits that neither, MacLeod et al. or Janssens et al. suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids. Consequently, applicants' attorney respectfully submits that the presently claimed composition unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record. Accordingly, applicants' attorney respectfully submits that the present invention is patentable over the art of record.

Fees

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 10-0750/PRD2077USNP/HBW.

Request for Allowance

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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